UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte MONTY KRIEGER

Appeal 2007-4148
Application 09/148,012
Technology Center 1600

Decided: September 25, 2007

Before TONI R. SCHEINER, DONALD E. ADAMS, and ERIC GRIMES, *Administrative Patent Judges.*

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of inhibiting pregnancy or treating steroid-related diseases. The Examiner has rejected the claims as nonenabled and lacking an adequate description in the Specification. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

BACKGROUND

"Scavenger receptors mediate the endocytosis of chemically modified lipoproteins, such as acetylated LDL (AcLDL)" (Specification 2). "Hamster

and murine homologs of SR-BI, an AcLDL and LDL binding scavenger receptor . . . ha[ve] been isolated and characterized" (*id.* at 5).

"Direct binding studies show that SR-BI expressed in mammalian cells . . . binds HDL, without cellular degradation of the HDL-apoprotein, and lipid is accumulated within cells expressing the receptor" (*id.* at 6).

> SR-BI . . . mediates the uptake and transport of cholesteryl ester from high density lipoproteins. It has been demonstrated that transgenic animals which do not produce SR-BI are healthy, with the exception that the females are infertile. This provides evidence that inhibition of uptake, binding or transport of cholesteryl ester to SR-BI can be used to inhibit pregnancy. The same pathway can also be used to decrease production of steroids, and therefore be used as a therapy for disorders involving steroidal overproduction.

(*Id.* at 7.)

DISCUSSION

1. CLAIMS

Claims 1-9, 12, 15, 16, and 20-22 are on appeal. Claim 19 is also pending but has been withdrawn from consideration by the Examiner.

The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). We will focus on claim 1, the broadest claim on appeal. Claim 1 reads as follows:

> 1. A method for inhibiting pregnancy or decreasing production of steroids in a mammal comprising
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> administering a compound inhibiting uptake, binding or transport of cholesteryl ester by SR-BI in the mammal in an amount effective to inhibit pregnancy or to decrease production of steroids in disorders involving steroidal overproduction.

2. WRITTEN DESCRIPTION

Claims 1-9, 12, 15, 16, and 20-22 stand rejected under 35 U.S.C. § 112, first paragraph, on the basis that the

> claims a[re] drawn to methods which potentially use a universe of compounds. However, Appellant has only provided written description of a small number of specific compounds which act via SR-BI, including estrogen (Example 3 on pages 39-40 of the specification), adenoviral vector encoding SR-BI (Example 5 on pages 40-45 of the specification), and anti-SR-BI antibody (Example 8 on pages 55-66 of the specification) to alter cholesterol levels.

(Answer 3.) The Examiner finds that the Specification does not provide an adequate written description of the claimed method (*id.* at 2-3).

We agree with the Examiner that the Specification does not adequately describe the claimed method. Describing a claim to a method requires describing the compounds used in the method. *See University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926 (Fed. Cir. 2004). Here, claim 1 requires use of a compound that inhibits uptake, binding, or transport of cholesteryl ester by SR-BI. The Specification therefore must adequately describe that genus of compounds.

A chemical genus can be described by structural description of a representative number of the species within the genus or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997). The structural description does not necessarily require disclosure of the compound's complete chemical structure:

> [T]he written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964, (Fed. Cir. 2002) (emphasis omitted, bracketed material in original).

Here, claim 1 is directed to a method comprising administering a compound that inhibits uptake, binding, or transport of cholesteryl ester by SR-BI in order to inhibit pregnancy or decrease steroid production.

The Specification states that such inhibitors

> include nucleotide molecules such as antisense oligonucleotides, ribozymes, and triplex forming oligonucleotides which bind to the SR-BI gene, either the protein encoding region of the gene or the regulatory regions of the gene; small organic molecules which bind to the SR-BI protein; soluble SR-BI protein or fragments thereof which competitively bind to the substrate for cell bound SR-BI; and compounds which block binding of HDL to SR-BI.

(Specification 11.)

The Specification also describes several assays that are said to be useful "to screen for compounds which are effective in methods for alter[ing] SR-BI expression, concentration, or transport of cholesterol" (*id.* at 14: 21-23; the assays are described on pages 14-17). The Specification also describes in general terms how to randomly generate "receptor or receptor encoding sequence binding molecules (*id.* at 18-19), computer assisted drug design (*id.* at 19-20), generation of "nucleic acid regulators" such as antisense RNA and triplex-forming oligonucleotides (*id.* at 20-24),

and preparation of receptor protein fragments (*id.* at 24-25). Finally, the Specification describes a working example in which antibodies to "mSR-BI" (murine SR-BI; *id.* at 40: 26) were raised and combined *in vitro* with SR-BI-expressing adrenocortical cells to determine the effect of the antibody on HDL uptake and steroid production (*id.* at 55-66).

Thus, the Specification does not describe any structural features that are shared by compounds having the function of "inhibiting uptake, binding or transport of cholesteryl ester by SR-BI." The Specification describes two polyclonal antibody preparations that contain antibodies to murine SR-BI. The Specification discloses the amino acid sequence of murine SR-BI (SEQ ID NO: 4), and therefore the disclosed antibodies are adequately described. *See Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004).

However, the Specification describes no other specific compounds having the function of "inhibiting uptake, binding or transport of cholesteryl ester by SR-BI." The present case is therefore analogous to *Rochester*. In that case, the patent claimed a method of selectively inhibiting the enzyme PGHS-2 (also known as COX-2) by "administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to a human." 358 F.3d at 918. The patent "described in detail how to make cells that express either COX-1 or COX-2, but not both . . . , as well as 'assays for screening compounds, including peptides, polynucleotides, and small organic molecules to identify those that inhibit the expression or activity of the PGHS-2 gene product.[']" *Id.* at 927.

The court held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the

desired activity: without disclosure of *which* peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims were not adequately described. *See id.* ("As pointed out by the district court, however, the '850 patent does not disclose just 'which "peptides, polynucleotides, and small organic molecules" have the desired characteristic of selectively inhibiting PGHS-2.' . . . Without such disclosure, the claimed methods cannot be said to have been described.").

Just as in *Rochester*, the present application discloses several genera of chemical compounds ("nucleotide molecules such as antisense oligonucleotides, ribozymes, and triplex forming oligonucleotides . . . ; small organic molecules . . . ; soluble SR-BI protein or fragments thereof . . . ; and compounds which block binding of HDL to SR-BI") and assays for screening such compounds to identify those having the desired activity. And, just as in *Rochester*, the present Specification does not disclose *which* of the many candidate compounds have one of the recited activities. The *Rochester* court held that such a disclosure does not adequately describe a genus of compounds required to practice a claimed method.

Granted, the present case differs from *Rochester* in that the present Specification describes antibodies to murine SR-BI, one of the compounds having the activity recited in claim 1. That disclosure, however, does not adequately distinguish the instant case from *Rochester*, because Appellant has not shown that the antibody is representative of the entire genus of compounds having the recited activities or that it shares "structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Cf. Eli Lilly*, 119 F.3d at 1569.

Appellant argues that, in addition to antibodies that bind murine SR-BI, the Specification describes adenoviral vectors that encode SR-BI and transgenic animals made by inactivating SR-BI in embryonic stem cells (Br. 8-9).

These disclosures do not contribute to the description of the claimed method. Adenoviral vectors encoding SR-BI result in overexpression of SR-BI, the opposite effect from that required by claim 1. (Specification 40: 26-29 (mice infected with an SR-BI-encoding adenovirus transiently overexpress SR-BI).) Inactivating the SR-BI gene in transgenic animals results in "inhibiting uptake, binding or transport of cholesteryl ester by SR-BI," but Appellant has not begun to explain how this method could be practiced on a living, mammalian patient – as required by claim 1 – who can hardly be generated from embryonic stem cells.

Appellant also argues that "the many compounds that already exist for regulating cholesterol levels . . . can be used to inhibit pregnancy or decrease steroidal overproduction via the modulation of SR-BI expression or activity" (Br. 9). Appellant argues that a "different degree of description is required where compounds are known and one only needs to provide the criteria for their selection and use – a degree clearly met by appellant" (*id.* at 10).

We do not find this argument persuasive. The record provides no basis to expect that compounds that lower plasma cholesterol levels would inhibit SR-BI activity, since elimination of SR-BI activity results in *elevated* plasma cholesterol. (Specification 50:10-13.) Those skilled in the art would therefore expect that inhibition of SR-BI activity by an administered compound would also result in elevated plasma cholesterol levels.

In addition, even though inhibiting SR-BI was shown to increase plasma cholesterol levels in transgenic mice, it does not follow that increasing cholesterol level in a patient having normal SR-BI function will inhibit SR-BI, and thereby inhibit pregnancy. Appellant has pointed to no evidence in the record that would show that SR-BI is down-regulated or inactivated in response to elevated cholesterol levels. Thus, the evidence of record does not support Appellant's apparent position that any compound that elevates cholesterol will inhibit SR-BI.

We affirm the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description. Claims 2-9, 12, 15, 16, and 20-22 fall with claim 1.

4. ENABLEMENT

Claims 1-9, 15, 16, and 20-22 stand rejected under 35 U.S.C. § 112, first paragraph, on the basis that the Specification "does not reasonably provide enablement for any method of decreasing production of steroids or inhibiting pregnancy in a mammal" (Answer 3).[1] The Examiner reasons that

> Appellant has provided no guidance and working examples of any compounds which act via SR-BI to alter pregnancy other than those in knockout infertile female mice. In fact, the specification, estrogen . . . , adenoviral vector encoding SR-BI . . . , and anti-SR-BI antibody . . . have only been shown to

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[1] Claim 12 was also subject to this ground of rejection in the Office action mailed August 15, 2005 but was not included in the statement of rejection in the Examiner's Answer. At the same time, the Examiner did not expressly indicate that the rejection had been withdrawn with respect to claim 12. If this application is subject to further prosecution, the Examiner should consider whether claim 12 should be rejected for nonenablement.

> affect SR-BI and to alter cholesterol and lipoprotein levels, but have not been shown to inhibit pregnancy in a mammal.

(Answer 4.) The Examiner also finds that the exemplified "method of knocking out a gene in an embryonic stem cell is not comparable to a method of altering fertility . . . in a developed mammal" (*id.*).

The Examiner concludes that, because of the paucity of guidance and working examples, and the "lack of predictability as to which compounds affecting steroid levels will inhibit pregnancy, . . . undue experimentation is necessary to practice the claimed invention" (*id.* at 5).

We agree with the Examiner that the Specification does not provide sufficient guidance to enable practice of the full scope of the claimed method without undue experimentation. The Specification discloses that transgenic mice that do not express SR-BI at all are infertile; the Specification discloses no other examples of inhibiting pregnancy by inhibiting SR-BI. The Specification provides no guidance regarding what level of SR-BI expression above zero is sufficient to inhibit pregnancy.

The Specification provides no guidance or working examples that would enable those skilled in the art to achieve 100% inhibition of SR-BI in a developed animal expressing SR-BI. The Specification's example showing *in vitro* inhibition of SR-BI activity describes using SR-BI-binding antibodies to achieve up to 85% inhibition of HDL uptake (Specification 62: 26-28), up to 70% inhibition of HDL-selective cholesteryl ester uptake (*id.* at 63: 26-28), and up to 50% inhibition of cell association with HDL (*id.* at 64: 12-14), and up to 78% inhibition of steroid production (*id.* at 65: 21-23) in murine adrenocortical cells. The record provides an inadequate basis on which to extrapolate these *in vitro* results to what could be achieved *in vivo*,

and does not indicate whether this level of inhibition would inhibit pregnancy if achieved in a mammalian subject.

Thus, while the Specification provides a working example describing inhibition of SR-BI activity *in vitro*, it provides no working example of the method defined by claim 1: inhibiting pregnancy or decreasing production of steroids in a mammalian subject *in vivo*. The Specification also provides inadequate guidance regarding what level of SR-BI inhibition is required to inhibit pregnancy and what compounds can be administered to achieve the required inhibition.

"Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. . . . Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997).

While the Specification does disclose a possible connection between female fertility and SR-BI, it does not provide adequate guidance to enable those skilled in the art to inhibit pregnancy by inhibiting SR-BI activity without undue experimentation. We therefore agree with the Examiner that the Specification does not provide an enabling disclosure in compliance with 35 U.S.C. § 112, first paragraph.

Appellant argues that the working examples in the Specification support the instant claims, and that the Miettinen paper "showing restoration

of fertility by administration of a cholesterol lowering drug, probucal, . . . provides further support for the claimed method." (Br. 13.)

We do not agree that the Specification's examples or the Miettinen paper[2] provide an enabling disclosure. The Specification's examples show only that an SR-BI-binding antibody can inhibit some of the activity of SR-BI in cells *in vitro*; they do not show that that level of inhibition inhibits pregnancy or even that it can be achieved in a mammalian subject. None of the other examples substantively contribute to the enablement of the method defined by claim 1.

The Miettinen paper does not supply the enabling guidance missing from the Specification. First, Miettinen was published after the effective filing date of the present application and therefore can be relied on only to confirm assertions made in the Specification. *See In re Glass*, 492 F.2d 1228, 1232 (CCPA 1974) ("[A]pplication sufficiency under § 112, first paragraph, must be judged as of its filing date. It is an applicant's obligation to supply enabling disclosure without reliance on what others *may* publish after he has filed an application on what is supposed to be a completed invention. If he cannot supply enabling information, he is not yet in a position to file." (emphasis in original)). The Specification does not assert that drugs that affect plasma cholesterol levels, without affecting SR-BI activity, can inhibit pregnancy. In addition, as discussed above, Appellant has pointed to no evidence in the record that would show that cholesterol-

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[2] Miettinen et al., "Abnormal lipoprotein metabolism and reversible female infertility in HDL receptor (SR-BI)-deficient mice," Journal of Clinical Investigation, Vol. 108, pp. 1717-1722 (2001).

lowering or cholesterol-raising drugs affect the expression or activity of SR-BI.

Appellant also argues that "one of skill in the art would understand from the specification which compounds to use, and how to derive appropriate doses with minimal routine experimentation to practice the claimed method and inhibit fertility or treat a disorder characterized by excessive steroidal production." (Br. 13.)

Appellant provides no further explanation of the basis for this assertion. For the reasons discussed above, we disagree that the Specification provides adequate guidance to enable practice of the full scope of claim 1 without undue experimentation. The rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement is affirmed. Claims 2-9, 15, 16, and 20-22 fall with claim 1.

OTHER ISSUES

If this application is subject to further prosecution, the Examiner should consider the following issues:

A. Estrogen as SR-BI inhibitor

The Specification states that estrogen administration reduces SR-BI expression and is therefore an SR-BI inhibitor:

> Animals receiving estrogen had significantly reduced levels of SR-BI expressed in the liver, and elevated levels of SR-BI and fluorescence in the ovaries. Since administration of estrogen is associated with a number of side effects, inhibition is more preferably achieved through the use of agents which inhibit expression of SR-BI, translation of SR-BI, binding of SR-BI, or cellular processing mediated by the SR-BI.

(Specification 10: 29 to 11: 6.)

The prior art teaches methods of inhibiting pregnancy comprising administering estrogen. See, e.g., Spona et al., "Inhibition of ovulation by an oral contraceptive containing 100 μg levonorgestrel in combination with 20 μg ethinylestradiol," Contraception, Vol. 54, pp. 299-304 (1996) (of record).

Some of the claims were rejected earlier in prosecution as anticipated by Spona and other references. Those rejections were overcome by amendments to the claims, but the amendments that overcame the rejections have since been modified. Claim 1, as it currently stands, appears to read on the method disclosed by Spona. Other claims may also read on Spona, or other prior art.

If this application is subject to further prosecution, the Examiner should consider whether the claims as they currently stand are anticipated by, or would have been obvious in view of, methods taught in the prior art.

B. Claims 4-7

Claim 1, on which all the other claims depend, is directed to a "method . . . comprising administering a compound inhibiting uptake, binding or transport of cholesteryl ester by SR-BI." Claim 4 is directed to the same method "wherein the compound *decreases* SR-BI expression," while claim 5 is directed to the same method "wherein the compound *increases* SR-BI expression." Similarly, claim 6 is directed to the same method "wherein the compound *decreases* SR-BI binding to lipoprotein," while claim 7 is directed to the same method "wherein the compound *increases* SR-BI binding to lipoprotein."

If this application is subject to further prosecution, the Examiner should consider whether compounds having diametrically opposed mechanisms – both increasing and decreasing SR-BI expression, or both increasing and decreasing SR-BI binding to lipoprotein – can all have the same overall effect of inhibiting uptake, binding or transport of cholesteryl ester by SR-BI., as required by claim 1.

C. Claim 16

Claim 16 depends on claim 11, which has been cancelled. If this application is subject to further prosecution, the dependency of claim 16 should be corrected.

SUMMARY

We affirm the rejection of claims 1-9, 12, 15, 16, and 20-22 for lack of adequate written description and the rejection of claims 1-9, 15, 16, and 20-22 for lack of enablement.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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